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20 April 2005

Re: Reporting of Adverse Events to Institutional Review Boards; Public Hearing [Docket No. 2005N-0038]

To: FDA Dockets@oc.fda.gov

Dear Officer-in-Charge:

Please find attached the written comments from Eli Lilly and Company regarding Reporting of Adverse Events to Institutional Review Boards.

Yours truly,

Vish S. Watkins

Vish S. Watkins, MD
Global Product Safety
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Comments to FDA Docket on IRB Review of Adverse Event Reports

Introduction

On 21 March 2005, the FDA held a public hearing (Docket No. 2005N-0038) to discuss the process by which adverse events are reported to and reviewed by Institutional Review Boards (IRBs). Some of the key concerns from FDA, the IRB community, and others involve the high volume of individual adverse event reports that IRBs receive for multi-center studies, the usefulness of information received in this format, and the value and capability of IRBs in conducting this type of ongoing assessment of individual case reports during a clinical trial.

The notice of public hearing indicated that the sheer volume and nature of these reports have overwhelmed the ability of the IRBs to utilize these reports in any meaningful way. In addition, several participants questioned whether individual adverse events are informative enough to permit assessment of clinical implications, because the reports lack context, are often blinded to treatment, and mingle the truly significant events with those that are minor and not individually meaningful.

At the hearing, some key points of consensus emerged and some questions also were raised that need to be resolved.

Key Points of Consensus From The 21 March 2005 FDA Public Hearing

1. The reporting of large volumes of individual adverse event reports to IRBs does not provide them with meaningful support for their responsibility to conduct a continuing review of safety information at intervals appropriate to the degree of risk.

2. The principal investigators face the same difficulties encountered by IRBs in assessing large numbers of individual adverse events.

3. The recommendations of the Council for International Organizations of Medical Sciences Working Group VI (CIOMS VI) on managing safety information in clinical trials, which will be published shortly, addresses this topic and suggests solutions. The CIOMS VI recommendations include eliminating routine expedited mailing of adverse events to investigators and IRBs, and instead providing periodic line listings along with a summary report of the safety profile

for each drug. If IRBs or investigators desire additional information, it would be provided.

4. Lilly's presentations as well as the presentations from the CIOMS VI Working Group representatives discussed these recommendations at the hearing.

5. According to these recommendations:

   a. Sponsors should continue the practice of expedited reporting of serious, unexpected adverse drug reactions to regulatory agencies.

   b. Sponsors would eliminate the current practice of routine expedited case reporting to both investigators and IRBs.

   c. Individual case reports should be sent to IRBs on an expedited basis (at the same time that the report is submitted to the FDA and to investigators) only when the individual report is clinically meaningful. This decision should be made on the basis of clinical judgment, the seriousness of the event, strength of the evidence for causality, and impact on safety – examples include serious hepatotoxicity, aplastic anemia, fatal or life-threatening anaphylaxis.

   d. Sponsors should provide periodic analyses of safety to IRBs that include summary assessments of the safety profile of drugs based on cumulative safety data, along with a line listing of the routine expedited serious adverse event reports that were sent to regulatory agencies. The frequency of these reports would be based upon the characteristics of the individual compound (e.g., quarterly or other appropriate time-intervals). These reports and line listings would also be sent to regulatory agencies.

Questions That Emerged From The Public Hearing And Lilly's Answers

Question 1 and Response

Question 1
What is the role of the IRB as it relates to the review of safety information collected during the clinical trial?

Response to Question 1

It is a fundamental responsibility of the sponsor to monitor safety data as it is received from the investigators and to keep the FDA and participating investigators informed of any significant safety findings ((21 C.F.R. §§ 312.32, .55 and .56). FDA regulations are also clear that investigators are responsible from a medical standpoint for protecting the safety of their subjects, for notifying the IRB of all unanticipated problems involving risks to the subjects, and for updating the informed consent with significant new safety information (21 C.F.R. §§ 50.25 and 312.60 and .66).

For drug trials there are two regulations that clarify the IRB's role after initial approval of the trial: 21 C.F.R. § 56.108(b)(1) requires the IRB to ensure prompt reporting of "unanticipated problems involving risks to human subjects" and § 56.109(f) requires the IRB to review the research at appropriate "intervals." 21 C.F.R. Part 56 does not require routine review of individual case reports by IRBs. Rather, regulatory obligations of the IRBs would be much better served by receiving only the truly meaningful individual reports, plus aggregate data and analyses periodically as Lilly, CIOMS VI, and others have proposed. The IRB's authority to request additional information from sponsors provides additional protection.

Question 2 and Response

Question 2

Is there a difference in information that an IRB should receive from the investigator site for which it is responsible, as opposed to reports from other "external" sites?

Response to Question 2

For purposes of federal regulation there should be no difference. The IRB's role, as defined by the regulations discussed above, is not furthered by routine review of individual adverse event reports, whether those reports come from the local site or an external site.

An investigator has an individual regulatory responsibility for the safety of the subjects participating in the research study under his or her care. The IRB's responsibility, as referred to above, is to review the research at appropriate intervals. For liability or other reasons, the investigator's institution may want to provide oversight to ensure the investigator is fulfilling his or her responsibility. Whether or not the institution chooses to do that, and whether that oversight responsibility is placed on an IRB or another body, is a matter for the institution to decide. It would not change the statutory role of the IRB.

Question 3 and Response

Question 3

Should Data Monitoring Committees (DMCs) be required for all studies, and should all recommendations or reviews be sent to IRBs?

Response to Question 3

Some presenters raised the question whether DMCs should be responsible for periodic review of serious adverse events.

In November 2001, the FDA issued a Draft Guidance on Establishment and Operation of Clinical Trial Data Monitoring Committees, which discusses the factors to consider in determining whether a clinical trial should include a DMC.

The FDA Draft Guidance made the following points:

- All clinical trials require safety monitoring (21 CFR 312.32(c)), but not all trials require monitoring by a formal committee external to the trial organizers and investigators.
- DMCs have generally been established for large, randomized multisite studies that evaluate interactions intended to prolong life or reduce risk of a major adverse health outcome.
- DMCs should be established for controlled trials with mortality or major morbidity as a primary or secondary endpoint.
- Although DMCs may prove valuable in other settings as well, a DMC is not needed or advised for every clinical study.
- A trial that is large, of long duration, and multi-center raises more possibilities for safety concerns because of the greater overall exposure and because prolonged exposure may cause adverse effects not readily recognized as such. DMCs may be more important in these trials.
- If the trial is likely to be completed quickly, a DMC might not have an adequate opportunity to contribute.
- Although a DMC should always review summary adverse event data, it will not usually review in detail every adverse event reported.
- The involvement of a DMC in the review of individual adverse event reports will vary from situation to situation.

For the following reasons, DMCs would not be a solution to resolving the concerns regarding the large volumes of unaggregated adverse event reports received by IRBs:

- DMCs are of most help in specific situations as outlined in the FDA Draft Guidance and summarized above. These situations usually involve considerations of specific statistical endpoints, risk to trial participants, practicability of DMC review, and scientific validity.
- It is not practicable or necessary to appoint DMCs for every clinical trial just to review periodic safety reports for every drug in every clinical trial.

- It is likely that the numbers of academic and industry-sponsored clinical trials are so large that there would be serious practical limits to recruitment of DMC members and chairmen.

If a safety assessment by a DMC occurs during the course of a trial that results in a recommendation that has a significant impact on the clinical trial such as a change to the informed consent or a protocol amendment, the sponsor would then report this recommendation to the FDA, IRBs and investigators.

The FDA Draft Guidance states the following:

"Sponsor should notify FDA and the responsible IRBs of any recommendations or requests made by a DMC to the sponsor that address safety of participants-for example, recommendations to lower the dose of a study agent because of excess toxicity, or to inform current and future trial participants of an emerging safety concern that had not been recognized at the start of the trial. Such recommendations would always be presumptively based on findings that would meet the definition of a serious and unexpected adverse event. When mutually agreed to by the sponsor and the DMC, a DMC may be delegated responsibility for reporting directly to FDA, although in most cases the sponsor will make such reports."

Question 4 and Response

Question 4

Should investigators make the determination as to what adverse event reports to forward to IRBs?

Response to Question 4

Current regulations require sponsors to send all expedited serious adverse event reports from all study sites to all participating investigators. Investigators would be expected to have the same difficulties as IRBs in sifting through the high volumes of unaggregated individual adverse event reports to determine the truly meaningful information to forward to the IRBs. A more reasonable approach would be recommendations of the CIOMS VI Report, that the sponsor should determine which individual reports are individually meaningful and send only those individual reports to the investigator, in addition to summary analyses, as discussed above. Insofar as this proposal would limit the number of individual adverse event reports that sponsors send to investigators, this would require a change in FDA regulations (e.g., 21 C.F.R. § 312.32).

Question 5 and Response

Question 5

Should sponsors send information directly to IRBs or should this information be sent to investigators to be forwarded to IRBs?

Response to Question 5

Sponsors should continue to forward the appropriate information to investigators, who are then responsible for forwarding the information to IRBs. The principal investigator at a particular site is the party directly responsible to the local IRB for safety of that trial. IRB representatives agreed with this approach, saying they want and need their local expert (the PI) to put the information into context. Maintaining these existing lines of communication will continue to allow sites to control exactly how information is forwarded to IRBs, keep IRBs independent of sponsor communications, and require fewer changes in process.

Question 6 and Response

Question 6

What should be the standard (or interpretation of the standard) for drug-relatedness that triggers an obligation for the sponsor to submit an expedited adverse event report?

Response to Question 6

Lilly believes that FDA should not consider modifications to criteria for expedited reporting as a part of this docket. The definition of an event that is serious, unexpected and associated with the use of the drug is being addressed separately as a part of FDA's proposed revisions to safety reporting regulations (the "Tome"). Modifying this definition might change (under the Tome, probably increase) the number of adverse event reports received by investigators and IRBs, but does not change the analysis of the relative value of reporting these events (under any definition) to IRBs or the above recommendations.

Conclusions

- Lilly agrees with the concerns of IRBs, FDA and others about the need to improve the process by which IRBs receive and review safety information for clinical trials.
- To address these concerns, Lilly suggests that the recommendations of the CIOMS VI Working Group's Report's Chapter 7 be a framework upon which these issues can be resolved:

  - Sponsors would continue sending expedited serious adverse event reports to the FDA on a routine basis
  - Sponsors would eliminate routine mailing of all expedited serious adverse event reports to IRBs and investigators
  - Sponsors would provide FDA, investigators, and IRBs with periodic safety reports that will comprise a line listing of expedited serious adverse event reports and a summary analysis of safety data at a frequency determined appropriate for each compound (e.g., quarterly)
  - Sponsors would send individual expedited adverse event reports to investigators and IRBs only when individually meaningful based on clinical judgment, seriousness of event, strength of evidence for causality, and impact on safety.
- Routine use of Data Monitoring Committees is not practicable or necessary for every clinical trial. Where a DMC is in place, recommendations regarding safety that have a significant impact upon the study, such as a change to the study protocol or to the informed consent document, should be communicated to the FDA and to the investigators and IRBs.
- The criteria for drug-relatedness that trigger a submission of expedited adverse event report should not be changed as part of this docket.

Lilly thanks the FDA for providing the opportunity to comment on this important topic.